

## **REMARKS**

Applicants have cancelled Claims 53-86 without disclaimer or prejudice, as being drawn to non-elected inventions. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuation or divisional applications.

Applicants also have amended Claims 6 and 24 for clarity. Enabling support for the amendments can be found in the application as filed, and therefore, no new matter is contained in the amendments and additions. Reconsideration of the present application and allowance of resulting Claims 1-52 and 87-94 is respectfully requested in view of the amendments and following remarks.

### **I. Election/Restriction Requirement**

The Office Action acknowledged Applicants' election with traverse of Group I (Claims 1-4, 8-31, and 37-52) and found the traversal persuasive with respect to Groups I-V and VIII. Therefore, the Office Action withdrew the restriction requirement with respect to Groups I-V and VIII and made the requirement final with respect to Groups VI, VII, and IX.

The Office Action examined together the claims of Groups I-V and VIII (Claims 1-52 and 87-94). Accordingly, Applicants have cancelled Claims 53-86 without disclaimer or prejudice as being drawn to non-elected inventions. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuation or divisional applications.

### **II. Rejection Under 35 U.S.C. § 112, Second Paragraph**

The Office Action rejected Claims 6 and 24 under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully submit that the claims as amended particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Claim 6 was rejected as being indefinite because it was unclear whether the claim was intended to depend from Claim 5. Applicants have amended Claim 6 to indicate that it depends from Claim 1.

Claim 24 was rejected as being indefinite in the recitation of the phrase "transfer donor or acceptor" because it was unclear what moieties Applicants were claiming to be compatible with the instant invention. Applicants have amended Claim 24 to delete the phrase "resonance energy transfer donor or acceptor moiety" and to now recite "resonance energy transfer donor moiety; resonance energy transfer acceptor moiety." Applicants respectfully submit that the specification discloses moieties that would be compatible with the present invention at paragraphs [065]-[068] on pages 22-24. In particular, the specification discloses that the resonance energy transfer moieties may be fluorescence resonance energy transfer (FRET) moieties or luminescence resonance energy transfer (LRET) moieties. The specification further discloses specific suitable moieties (paragraph [078] on pages 26-28), and Applicants respectfully submit that one of ordinary skill in the art would readily know additional FRET and LRET moieties that would be compatible with the instant invention.

Applicants respectfully submit that the present amendments to the claims and arguments made overcome these rejections under § 112, second paragraph. Accordingly, Applicants respectfully request that the rejections under § 112, second paragraph be withdrawn.

### **III. Rejection Under 35 U.S.C. § 103(a)**

The Office Action rejected Claims 1-8, 11-19, 21-27, 39-37, 40-45, 47-52, 87, 89-91, 93, and 94 under 35 U.S.C. § 103(a) as being unpatentable over Kresse et al. (U.S. Patent No. 6,576,221). In particular, the Office Action asserted that Kresse et al. disclose iron-containing nanoparticles having a primary polymer coating and a secondary targeting polymer coating, and optionally adjuvants, pharmaceuticals, and/or adsorption mediators/enhancers. The Office Action further asserted that Kresse et al. disclose that the iron containing core has a magnetic moment greater than that of iron (II) or iron (III) ions (facilitating the contrast enhancing effect when the substance is used as a contrast material for magnetic resonance tomography) and may consist of magnetite or maghemite. The Office Action asserted that Kresse et al. disclose adsorption mediators/enhancers including peptides; complexing and chelating agents; paramagnetic metals for use in the generation of the iron-containing nanoparticles; targeting agents, including proteins, peptides, polypeptides, antibodies, antibody fragments,

oligonucleotides, DNA, and RNA; and various possible applications in magnetic resonance angiography, perfusion imaging, infarct visualization, and for differential diagnosis of tumors/metastases from hyperplastic tissue. Accordingly, the Office Action asserted that it would have been obvious to one of skill in the art at the time of the invention to generate a nanoparticle composition comprising a detectable moiety having a coating thereon, a targeting moiety attached to the coating, and a delivery ligand attached to the coating because Kresse et al. disclose iron containing nanoparticles having a double coating that are useful for diagnostic and therapeutic purposes.

Applicants respectfully submit that Kresse et al. do not teach or suggest the present invention as claimed. More specifically, the present invention discloses magnetic nanoparticles for use in intracellular molecular imaging that contain both 1) at least one targeting probe and 2) an intracellular delivery ligand. These nanoparticle probes of the present invention provide high specificity and sensitivity, and enhanced signal-to-noise ratio in molecular imaging by providing the peptide-based intracellular delivery of probes and specific cell- or tissue-type targeting. Accordingly, these nanoparticles can be used for both optical intra-cellular imaging and deep-tissue molecular imaging using MRI.

The nanoparticle probes of the present invention comprise a detectable moiety comprising a magnetic nanoparticle having a biocompatible coating thereon. The nanoparticle probes further comprise at least one targeting probe (referred to below as "targeting/detection probe") that may be, *e.g.*, a nucleic acid, a polypeptide, an antibody or fragment thereof, a high affinity ligand, a peptide, or an aptamer that facilitates the detection of a particular molecule and/or its expression levels. *See* pages 18-32. The nanoparticle probes of the present invention further include an intracellular delivery ligand that facilitates the delivery of the nanoparticle across a cellular membrane or additionally across an intracellular organelle membrane. *See* page 15, paragraph [048]. In certain other embodiments of the present invention, the nanoparticles comprise a second ligand that is capable of interacting with a specific tissue, cell type, or disease-specific marker. *See* page 17, paragraph [050].

The Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. There must be a suggestion or motivation in the reference(s) to modify the

reference(s); there must be a reasonable expectation of success; and the prior art reference(s) must teach all of the claim limitations. *See* MPEP § 2143. Here, the Patent Office has not met this burden. The Patent Office has provided no evidence of a suggestion or motivation within the Kresse et al. reference to include both at least one targeting/detection probe and at least one intracellular delivery ligand on the nanoparticle. Further, even if one of skill in the art would have been motivated by Kresse et al. to modify the particles as disclosed in Kresse et al., there would be no expectation of success for executing this modification. Moreover, the Kresse et al. reference does not teach all of the limitations of the present invention.

Applicants respectfully submit that Kresse et al. do not teach or suggest a nanoparticle comprising a detectable moiety with a biocompatible coating thereon and both at least one targeting/detection probe and at least one intracellular delivery ligand. By contrast, Kresse et al. teach iron-containing nanoparticles having two coating layers, with the outermost layer consisting of a single delivery-related component, a "targeting polymer." This "targeting polymer" is a delivery vehicle that directs the *in vivo* behavior of the nanoparticle and allows the nanoparticle to be delivered to a particular cell or tissue. While the Office Action asserted that this targeting agent could be one of a number of molecule types (including, among others, peptides or nucleic acids), there is no teaching or suggestion in Kresse et al. that the addition of certain targeting/detection probes and/or additional targeting ligands (as currently disclosed) may be used to facilitate further specificity and sensitivity of the nanoparticles. In particular, the Kresse et al. reference does not disclose or suggest the requirement of two components to affect delivery of the nanoparticle and to allow for detection of a particular nucleic acid or polypeptide. Further, there is no teaching or suggestion that specific peptides could be used for the intracellular uptake of the nanoparticles as is required by the delivery ligand component of the present nanoparticle probes. The Kresse et al. reference does suggest that the nanoparticles may further comprise adsorption mediators/enhancers including peptides; however, such peptides are included to enhance the adsorption of the targeting agent to the nanoparticle or the primary coating and not to direct the delivery of function of the nanoparticle. *See* Column 8, lines 21-27 and Column 15, lines 24-44. Therefore, Applicants respectfully submit that the presently claimed invention would not be obvious to one of ordinary skill in the art. Even if the motivation

were provided for a magnetic particle with a biocompatible coating and both a targeting probe and a delivery ligand attached thereto, there is no suggestion of its successful use in traversing tissues to facilitate detection and imaging as shown in the Examples of the present disclosure.

For at least these reasons, the Office Action failed to establish a *prima facie* case of obviousness, and Kresse et al. do not teach or suggest the presently claimed invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

#### **IV. Conclusion**

Applicants believe that the present application, as amended, is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The foregoing is submitted as a full and complete response to the Office Action mailed February 6, 2006.

No additional fees are believed due at this time. However, please charge any fees that may be due, or credit any overpayment, to Deposit Account 19-5029 (Ref.: 17625-0058). In addition, if there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited and encouraged to call the undersigned attorney at (404) 853-8000.

Respectfully submitted,



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